REMARKS

Claims 1-44 and 85 are withdrawn. Claims 45, 48, 50-84 and 86-88 are under examination. The following addresses the Substance of the Office Action.

Election of Species

The Examiner has requested cancellation of the non-elected species from Claim 45. While Applicants agree with the Examiner that the claims are currently subject to an election of species in which the initial embodiment of the capture molecule to be searched is the embodiment where the capture molecule is a nucleic acid, Applicant respectfully argues that such amendment of Claim 45 at this time is not required. According to MPEP 803.02:

> In applications containing **>a Markush-type claim that encompasses at least two independent or distinct inventions<, the examiner may require a provisional election of a single species prior to examination on the merits. < Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, >the provisional election will be given effect and< examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended.

Therefore, Applicant asserts that there is no need to amend claim 45 by deleting the non-elected members of the Makush group.

Written Description

The Examiner has rejected Claims 45, 48, 50-84, and 86-88 under 35 USC §112, first paragraph as failing to comply with written description requirement. The Examiner has again stated that the disclosure allegedly fails to find adequate written description of the genera set forth in Claim 45. Currently pending claim 45 recites "nucleic acid probes are from nucleic acids encoding polypeptides, said polypeptides selected from the group consisting of enzymes, transcription factors, structural proteins, transporters, antibodies, antigens, receptors, markers of toxicity, bacterial markers, viral markers, oncogenes, tumor suppressors, senescence markers, tumor necrosis factors, proteins involved in apoptosis, inflammation, DNA damage and repair, oxidative stress, metabolism, and cell cycle". Applicant respectfully points the Examiner's attention to Tables 1-3 in the Specification which provide specific examples of the molecules

that can be used as capture molecules on the disc of the invention. The sequences, as attested by their GenBank Accession numbers listed in the Specification as filed, and functions of these molecules were known at the time the invention was made. For the Examiner's convenience we reproduce here Tables 2 and 3 from the Specification as filed:

Table 2: Sequences presented upon the HepatoChips with their known function and Genbank accession number

Gene	Function	Genbank Accesion no.
Bax, Bcl-2	Apoptosis	U49729, L14680
c-jun, c-myc, Elk-1	Oncogene	X17163, Y00396, X87257
Cox-2, IL6	Inflammation	L20085, M26744
Cyp 1A1, Cyp 1B1, Cyp 2B, Cyp 3A, Cyp 4A1	Cytochrome P450	X00469, U09540, M34452, M10161, X07259
Enoyl CoA hydratase, PPAR α	PP	K03249, M88592
ACO	PP Acyl CoA Oxidase	J02752
Ferritine	Iron Stock	U58829
Fibronectin	Extracellular Matrix	X15096
GADD153, GADD45	DNA Damage	U30186, L32591
MGMT	DNA Repair	M76704
Glutathione S-transferase Subunit Ya ,subunit theta 5	Oxidative stress	K01931, X67654
GSH Reductase, Heme Oxygenase 2, HSP70, MnSOD, ApoJ, Cytochrome C oxidase subunit 1	Oxidative stress	U73174, J05405, L16764, Y00497, M16975, M27315
Hepatocyte GF	Growth Factor	D90102
Histone D-acetylase (Hdac1)	DNA Transcription	NM008228
HMG CoA synthetase	Cholesterol Metabolism	X52625
JNK-1, Telomerase, Cyclin D1	Cell Cycle activation	L27129, U89282, D14014
NFκB, p38, erk-1, c/EBP, Iκβα	Transcription factor	L26267, U73142, M61177, X12752, U66479
Ornithine carboxylase (odc)	Arginine synthesis	J04791
P53	Tumour Suppressor	X13058
PCNA	Proliferation Cellular Nuclear Antigen	Y00047
Rmdr-1b, Transferrin, Albumin	Transporters	M81855, D38380, V01222
SMP30	Senescence Marker	X69021
TNF	Tumour Necrosis Factor	X66539
Transforming growth factor-b type II	TGF-beta receptor	L09653
UDPGT1A, UDPGT1A6	Glucuronyl Transferase	J05132, D83796
Liver +ve control	α2-macroglobulin	J02635

Table 3: HouseKeeping genes included on the Hepato CD

HouseKeeping Gene	Function	Abundance level	Accession number
α-Tubulin	Cytoskeletal protein	High	V01227
Ribosomal protein S29	Protein synthesis	Medium	X59051
Myosin heavy chain 1 (myr)	Muscle contraction	Low	X68199
Hypoxanthine guanine phosphoribosyl transferase	Nucleotide synthesis	Medium	M86443
Glyceraldehyde-3-Phopshate dehydrogenase(G3PDH)	Glycolysis	High	D16554
Polyubiquitin	Cellular metabolism, development	High	D00036
Phospholipase A2	Lipid metabolism	Low	X02231
β-actin	Cytoskeletal protein	High	V01217

These tables (middle columns) provides exact written support for the underlined limitations in Claim 45 reproduced on the previous page, while the GenBank Accession numbers support the written description of more than just four primer sequences. Additionally, as the Applicant argued previously, the EP 1 136 566 publication incorporated explicitly by reference in the Specification (page 7, lines 13-17) provides additional sequences of capture molecules (on pages 10, 11, 12, and 14). Altogether, the Specification provides written description of more than 60 sequences.

Furthermore, Applicants note that, as previously pointed out, the methodology disclosed in the specification for attaching the capture molecules to the disc is effective for any of the claimed types of capture molecules regardless of their sequence or structure. By analogy, just as the inventor of the Southern blot could satisfy the written description requirement for a claim to a nitrocellulose filter having a nucleic acid bound thereto without providing the sequences of all of the nucleic acids which could potentially be bound to the filter because the methodology for binding the nucleic acid to the filter is independent of the sequence of the nucleic acid, the present inventors also satisfy the written description requirement for the pending claims because the methodology for attaching the claimed types of capture molecules to the CD described in the specification is independent of the sequence or structure of the capture molecules.

The Examiner has rejected Claims 74-81 and 82-84 under 35 USC §112, first paragraph as failing to comply with written description requirement. Specifically, the Examiner indicated

that the Specification does not have adequate written description of the "detection and/or reading device" or the "handling device", including the software that is required for its operation. The rule under MPEP 2163 is that:

> "The description need only describe in detail that which is new or not conventional. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.
>
> Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention. See, e.g., In re Hayes Microcomputer Products, Inc. Patent Litigation, 982 F.2d 1527, 1534-35, 25 USPQ2d 1241, 1246 (Fed. Cir. 1992) ("One skilled in the art would know how to program a microprocessor to perform the necessary steps described in the specification. Thus, an inventor is not required to describe every detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains. Disclosing a microprocessor capable of performing certain functions is sufficient to satisfy the requirement of section 112, first paragraph, when one skilled in the relevant art would understand what is intended and know how to carry it out.").

Applicant respectfully points the Examiner's attention to page 4 of the Specification which teaches that the definition of a disk includes a CD or a DVD which comprise data that can be read by a CD-reading device. The rule is that the description need only describe in detail that which is new or not conventional. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. Here, the CD and DVD reading technology was already quite mature at the time the invention was made (December 30, 1997), as is apparent from the attached "History of CD Technology" (Exhibit 1) and as described in The CD-ROM Handbook, 2nd edition, The Complete Recordable CD Guide, and Digital Audio and Compact-disc Technology, 2nd ed. (referenced in the Specification as filed, page 16, lines 6-12). Therefore, the inventor did not have to describe in detail the "detection and/or reading device" or the "handling device", including the software that is required for its operation.

Applicants note that the components for making the claimed devices were known to those skilled in the art at the time the present application was filed. In particular, components such as lasers, mirrors, and photodiodes for detecting light were known in the art. The claimed devices are described throughout the specification and Figures, including at page 23, lines 10-32, page 24, lines 22-30, page 37, line 31-page 40, line 10, page 41, line 22-page 42, line 6, page 58, line 10-59, page, line 25, Example 13-15, and Figures 3-6 and 11-14.

Furthermore, if the Examiner is asserting that an actual computer program is required to satisfy a written description requirement, then, as discussed above, the rule is:

> In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention. See, e.g., In re Hayes Microcomputer Products, Inc. Patent Litigation, 982 F.2d 1527, 1534-35, 25 USPQ2d 1241, 1246 (Fed. Cir. 1992) ("**One skilled in the art would know how to program a microprocessor to perform the necessary steps described in the specification. Thus, an inventor is not required to describe every detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains. Disclosing a microprocessor capable of performing certain functions is sufficient to satisfy the requirement of section 112, first paragraph, when one skilled in the relevant art would understand what is intended and know how to carry it out.**" (emphasis ours)

Therefore, Applicant asserts that all currently pending claims have adequate written description in the Specification as filed.

Likewise, with respect to the handling device of Claims 82-84, Applicants maintain that the claimed device is described at pages 35, line 31-37, line 30, Examples 9, 10, and 12, and Figures 8-10 and that one skilled in the art would be able to make the claimed devices using components available as of the filing date of the present application.

Enablement

The Examiner has rejected claims 45, 48, 50-84 and 86-88 under 35 USC §112, first paragraph as allegedly non-enabled. Specifically, the Examiner stated that the specification does not reasonably suggest that applicant was in possession of the tremendous genera encompassed, and that the specification is silent as to how each of these various components to be used, and how the information derived from same is to be processed and interpreted. As discussed above, Applicants maintain that the claimed invention is fully described in the specification.

Furthermore, as the Applicant has previously argued, the Specification provides written description of more than 60 various molecules that can be attached to the CD by means of, for example, covalent binding (see pages 45-46 of the Specification as filed):

> "Preferentially, capture molecules are covalently fixed on the surface containing chemical groups able to bind them within a minute period and without any third coupling agents. These reactions include, but are not limited to aldehyde/amine, acrylate/amine, isothiocyanate/amine or thiol/thiol binding. Coupling can be obtained between chemical groups like the amine/carboxilic, thiol/amino, alcohol/amino and other couples of functional groups (see Zammatteo et al 2000 (Anal. Biochem. 280, 143-150 and the Pierce catalogue on bifunctional reagents for biological molecules coupling and attachment)."
>
> The acrylate/polyacrylate polymer is a preferred layer since it responds to the characteristic here above mentioned for the formation of a layer on the disc, the binding of the capture molecules, the treatment of the disc and the reading of the results.
>
> The olefine containing polymers may also be first oxidixed in order to form aldehyde groups on the surface of the disc thus allowing the covalent binding of the capture molecules. Preferably, the oxidation step of the surface of the solid support allowing the formation of aldehyde functions is obtained in the presence of low concentrations of permanganate and periodate in a buffered aqueous solution. Oxidation in aqueous solutions prevent dammages to the polycarbonalte polymer. Aminated capture probes are covalently fixed on the aldehyde groups throught Schiff base formation which is then reduced with NaBH4 for stabilisation of the linkage. Aldehyde groups are also preferentialy obtained by plasma deposition of acetaldehyde or acrolein vapor onto the surface of polymers.

See also, Example 1 on pages 47-48:

> *Amination of polycarbonate of CD*
>
> CD were first carboxylated by incubation 30 min in NaOH 1N solution at room temperature. After 3 washes with water, carboxylated CD were incubated in a solution of MES 0.1M pH 6 buffer containing water soluble carbodiimide at 1 mg/ml and N-methylpopane 1-3 diamine at 1 mM during 2 hours at room temperature. After 3 washes in MES 0.1M pH 6 buffer and 3 washes with water, the aminated CDs were dried at 37 ^{o}C for 30 min.
>
> *Binding of capture probes on aminated CDs*
>
> 2 solutions were prepared, one containing CMV capture probe and the other containing HIV capture probe. These solutions were MeIM 0.01 M pH 7.5 buffer containing denatured DNA capture probe (CMV or HIV) at a concentration of 2 µg/ml and carbodiimide at a concentration of 1.6 mg/ml.
>
> 3 x 20 µl of these solutions were spotted on two aminated CDs and these CDs were incubated at 50 ^{o}C for 5 hours in a wet atmosphere. After three washes

of 5 min with NaOH 0.4 N + Tween 0.25% at 50 ^{o}C, these CDs were rinsed 3 times with water and dried at 37 ^{o}C for 30 min.

Therefore, the starting materials are provided and described, how to attach them to the CD is described, how to detect the results of the reaction between the capture molecules attached to the CD and the target molecules (for example silver precipitation) are also described (Example 2, on page 49 and Example 8, on page 62-63, the latter is reproduced herein for the Examiner's convenience).

Hybrid detection

The presence of biotinylated hybrids on the microarray was detected using the colorimetric based labeling as in example 7. The Bio-CD was incubated at room temperature for 15 min in the Silver Blue Solution (AAT, Namur, Belgium), rinsed in water, dried 5' at 37°C and read with the Bio-CD reader. Results digitalized are quantified with softwares included in the CD-Reader as explained in example 7.

The intensity of each DNA spot (average intensity of each pixel present within the spot) was calculated using local mean background subtraction. A signal was deemed significant if the average intensity after background subtraction was at least 2.5 fold higher than their local background. The two intensity values of the duplicate DNA spots was averaged and used to calculate the intensity ratio between the reference and the test. Very bright element intensities (saturated signals, highly expressed genes) were deemed unsuitable for accurate quantification because they underestimated the intensity ratios and were excluded from further analysis.

The data obtained from different hybridizations were normalized in two ways. First the values are corrected using a factor calculated from the intensity ratios of the internal standard reference and the test sample. A second step of normalization was performed based on the expression levels of housekeeping genes. This process involves calculating the average intensity for a set of housekeeping genes, the expression of which is not expected to vary significantly. The variance of the normalized set of housekeeping genes is used to generate an estimate of expected variance, leading to a predicted confidence interval for testing the significance of the ratios obtained. Ratios outside the 95% confidence interval were determined to be significantly changed by the treatment.

Therefore, Applicant asserts that Claims 45, 48, 50-84 and 86-88 are fully enabled by the Specification as filed.

In addition, applicant provides the following proof of the existence of the commercial embodiment of the claimed invention: an on-line advertisement of a BioCD from the Eppendorf Array Technologies website (Exhibit 2); and a publication by Alexandre et al 2002 "Compact

Disc with both Numeric and Genomic Information as DNA Microarray Platform" BioTechniques 33:435-439 (Exhibit 3).

For the foregoing reasons, Applicants respectfully request that the enablement rejection be withdrawn.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of the above remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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